Negative Myoclonus Following Immune Checkpoint Inhibitor Therapy in a Patient with Lung Adenocarcinoma: Expanding the ICI-Toxicities Spectrum

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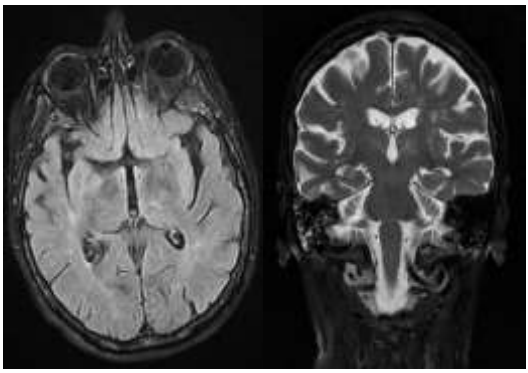
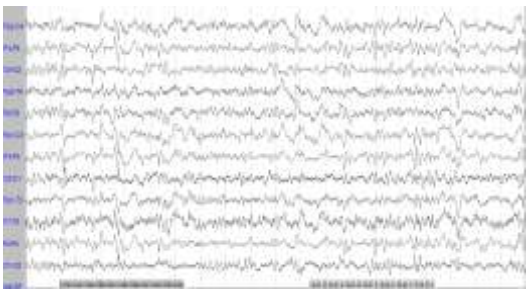
Background and introduction

Immune checkpoint inhibitors (ICIs) are highly effective monoclonal antibodies that target regulatory proteins of the immune system, known as immune checkpoints, to enhance immunity against cancer cells. This activation frequently results in immune-related adverse events immune-related adverse events that, in 1-3% of patients, can affect the nervous system[1].

Case Presentation

A 69-year-old female with stage IV pulmonary adenocarcinoma on pembrolizumab (anti-PD1) monotherapy presented with subacute onset of diffuse, stimulus-sensitive jerky movements affecting the trunk and limbs. Neurological examination confirmed multifocal, irregular interruptions in tonic muscle activity, consistent with negative myoclonus; no other abnormalities were detected. General blood tests, including liver and kidney function as well as electrolytes, did not reveal any significant abnormalities. Brain MRI was unremarkable, without evidence of structural lesions. Electroencephalography (EEG) showed generalized background slowing with diffuse and frequent spikes and sharp waves. Levetiracetam (500 mg BID) was therefore started due to a suspected cortical origin. No clinical or electrographic seizures were observed. Serum testing for intracellular neuronal antibodies, including anti-Hu, Yo, Ri, Ma2, and amphiphysin, was negative. Given the temporal association with immunotherapy and the absence of alternative etiologies, an immune-related movement disorder was considered. High-dose intravenous methylprednisolone (1g daily for 5 days) was administered, with partial neurological improvement. Unfortunately, the patient subsequently developed pulmonary embolism and septic shock, resulting in multi-organ failure and death.





Discussion

Immune checkpoint inhibitors can cause various neurological adverse events, including encephalitis, myelitis, aseptic meningitis, neuropathies, and movement disorders. Myoclonus is a rare but increasingly recognized manifestation; in particular, negative myoclonus has been reported in only one case as part of a mixed myoclonus presentation, with a good steroid response, besides with no EEG-correlate[2]. Another case report described a patient treated with atezolizumab (anti-PD-L1) presenting with an opsoclonus-myoclonus-ataxia syndrome that responded to steroid and IV immunoglobulins therapy[3]. Proposed mechanisms include autoimmune-mediated cortical or subcortical dysfunction, though often no structural correlate is seen on imaging, as in our case. Treatment with corticosteroids and/or IVIG generally leads to partial or full recovery, but mortality remains high when systemic complications coexist.

Conclusion

Negative myoclonus may represent a rare checkpoint-inhibitors related immune-mediated toxicity. Prompt recognition and immunosuppression are critical, although in our case systemic complications have influenced prognosis. Further research is needed to elucidate the pathophysiological basis and optimal treatment strategies for ICI-associated movement disorders.

References

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